Trends in mortality from intractable diseases in Japan, 1972–2004

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Key words : Intractable disease, death rate, joinpoint regression analysis, aplastic anemia, Parkinson's disease, systemic lupus erythematosus, ulcerative colitis, idiopathic thrombocytopenic purpura, polyarteritis nodosa, amyloidosis

Purpose In 1972, the Ministry of Health, Labour and Welfare of Japan defined intractable diseases as those with unknown etiology, no established treatment regimens, and severe sequelae of physical, mental and social difficulties. Since then, the Ministry has promoted scientific research on these diseases and offered financial support to those suffering from their effects. The purpose of the present study was to analyze trends in deaths from the diseases in Japan over the period from 1972–2004.

Methods For the selected intractable diseases with 100 deaths or more per year, crude (CDR) and direct age-standardized death rates (ADR) were computed using the national underlying-cause-of-death mortality database of Japan based on International Classification of Diseases. Joinpoint regression analysis was applied to identify significant changes in the trends.

Results The CDRs in the latest observed year per 1million persons/year) for males and females were 25.55 and 25.93, respectively, for Parkinson's disease, 5.41 and 6.92 for aplastic anemia, 0.87 and 3.50 for systemic lupus erythematosus, 2.93 and 2.36 for amyloidosis, 1.40 and 1.54 for polyarteritis nodosa, 1.34 and 1.61 for idiopathic thrombocytopenic purpura, and 1.02 and 0.74 for ulcerative colitis. The respective annual percentage changes (APCs) for males and females during the overall period decreased for ulcerative colitis (−5.2% and −7.5%), aplastic anemia (−3.6% and −3.7%), idiopathic thrombocytopenic purpura (−2.1% and −3.0%), and systemic lupus erythematosus (−0.9% and −2.6%), while the APCs increased for amyloidosis (+3.3% and +3.5%), polyarteritis nodosa (+3.2% and +4.0%), and Parkinson's disease (+0.7% in males alone). With the APCs in the latest trend phase, polyarteritis nodosa and Parkinson's disease in females showed appreciable declines; on the other hand, amyloidosis in males demonstrated the significant increase, and ulcerative colitis in males exhibited an apparent leveling off of the decline.

Conclusion The ADRs for most of the intractable diseases have declined significantly in Japan over the last 3 decades. The decline might be attributed in large part to improved diagnosis and treatment because of the lack of effective primary prevention measures. Support for the affected patients and further research on etiology and radical cure of the diseases must be considered necessary.

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ORIGINAL ARTICLE

Nutritional status and risk of amyotrophic lateral sclerosis in Japan

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Abstract

Only a few human studies have reported the relationship between dietary factors and the risk of amyotrophic lateral sclerosis (ALS). We therefore analyzed the relationship between macronutrients (carbohydrate, protein and fat) and the risk of ALS using a case-control study in Japan. The study comprised 153 ALS patients diagnosed by the El Escorial World Federation of Neurology criteria, and 306 gender- and age- matched controls randomly selected from the general population. A self-administered food frequency questionnaire was used to estimate pre-illness intakes of food groups and nutrients. The strength of association between ALS and a potential risk factor was assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs). A high intake of carbohydrate was significantly associated with an increased risk of ALS (adjusted OR=2.14, 95% CI 1.05–4.36; the highest versus the lowest tertile). ORs for the second and third tertile of total fat were 0.57 and 0.41 (95% CI 0.21–0.80), respectively. ORs for the highest tertile of intake versus the lowest were 0.41 (95% CI 0.21–0.80) for total fat, 0.30 (95% CI 0.16–0.5) for saturated fatty acids (SFAs), 0.35 (95% CI 0.18–0.69) for monounsaturated fatty acids (MUFAs) and 0.58 (95%CI 0.40–0.96) for polyunsaturated fatty acids (PUFAs). Our findings suggest that high intakes of carbohydrate and low intakes of fat and some kinds of fatty acids may, when combined, increased the risk of ALS.

Key words: *Amyotrophic lateral sclerosis, case-control study, diet, macronutrients*

Introduction

With the rapidly Westernized dietary habits and sedentary lifestyles over the past several decades in Japan, the number of amyotrophic lateral sclerosis (ALS) patients has increased (1). Several epidemiological studies have examined the risk factors of ALS; most have focused on physical activity (2–4), skeletal fractures (5) and heavy metal exposure at work (6–8). Recently, a few such epidemiological studies have examined the relationship between dietary factors and the risk of ALS; most have focused on intake of calcium and magnesium (9–10) and dietary antioxidants, particularly vitamin E (11). However, those findings failed both qualitatively and quantitatively to provide any evidence on dietary factors, because so very little is known about the relationship between those factors and the risk of ALS. To the best of our knowledge, no study has yet examined the relation of macronutrients (carbohydrate, fat, and protein) to ALS. Thus, using a food frequency questionnaire (FFQ), we focused on the pre-illness dietary risk factors for ALS and assessed them in a case-control study in a Japanese population.

Methods

Subjects and methods

Study populations. Case subjects were all definite or probable ALS patients aged 18 to 81 years who had been diagnosed based on the El Escorial World Federation of Neurology criteria (13) in medical centers in the Tokai area of Japan from 1 January 2000 to 31 December 2004.

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ALS was definite in 65% and probable in 35% of cases. All cases of progressive bulbar palsy (PBP) were included in this study, whereas familial progressive muscular atrophy was excluded. There was no evidence of coexisting Parkinson's disease or related disorders including multisystem atrophy.

We set up two community controls matched to each patient for age (±2 years), gender and residence based on electoral districts. They were randomly selected from among the general population in the same district as our case subjects based on the basic register of residents. Selection was carried out by a proportional simple random sampling, with stratification by gender and age groups, using the basic resident registry.

Data collection. We asked patients to recall their lifestyle during the three years before the onset of ALS, and community controls the same before their interview. When patients were unable to provide any information on their lifestyle and exposures because of their seriously impaired conditions or early death, proxies (mainly spouses) were interviewed. Standardized in-person interviews were conducted for patients and for their individually matched control. Only when this was not possible was a proxy interview performed. To minimize information bias, when a case's proxy to a case was interviewed, the control's proxy to the control was also interviewed even if the control was competent to be interviewed.

The institutional ethics committee of the Aichi Prefectural College of Nursing and Health approved the protocol before commencement of the study. All participants provided informed consent to a verbal explanation of the study protocol including next of kin for case subjects who were severely ill, unconscious, or dead as well as proxy respondents for control subjects.

Dietary information. Dietary information was obtained by a self-administered food frequency questionnaire (FFQ), consisting of 97 commonly eaten food and beverage items. This FFQ was validated for food groups by referring to four 4-day dietary records (DRs) among 88 men and women in central Japan, from 1996 to 1997 (14–15). The energy-gender-and age-adjusted test-retest correlation coefficients between the two FFQs administered at a one-year interval ranged from 0.34 to 0.78. The de-attenuated, energy-, gender- and age-adjusted correlation coefficients between the second FFQ and the DRs were larger than 0.40 for most food groups. Estimates of nutrient intake were computed using the Standard Tables of Food Composition in Japan, Fifth revised and enlarged edition (Science and Technology Agency, 2000).

Covariates such as demographic characteristics (age at diagnosis, gender) and risk factors were collected based on the responses to a structured questionnaire specifically designed for this case-control study. A behavior pattern was measured by a 10-item scale designed for a Japanese cohort by Maeda (16). Subjects who scored between 0 and 16 were considered to exhibit a non-type A pattern, which indicated a relaxed and easy-going individual, while those who scored 17 or greater were considered as type A, which denotes a set of characteristics that includes people who are excessively time-conscious, insecure in their status, highly competitive, hostile and aggressive, and incapable of relaxation (17). Smoking status was ascertained in relation to the number of cigarettes smoked per day during the year before the survey (onset of ALS/interview), and subjects were categorized into current smokers (at least one cigarette per day), ex-smokers (smokeless for at least one year before the survey), and never smokers, and was further classified into current smokers and non-smokers (including ex-smokers and never smokers). Body mass index (BMI) was calculated as a subject's weight (kg) divided by height (m) squared as a measure of obesity.

Statistical analysis

The differences in mean values or frequencies between ALS patients and controls were statistically examined by unpaired *t*-test, χ^2 test, or Mantel-extension test. The odds ratio (OR) and its 95% confidence interval (CI) were estimated using multiple conditional logistic regression models to access the strength of association between ALS and potential risk factors (18). Tests for trends in logistic regression analysis were performed by the exposure variable and treating the scored variables as a continuous one.

In the analysis of estimated nutrient intakes, all the nutritional variables were natural logarithmically transformed to improve their normality. Because the intake of most nutrients is strongly correlated with total energy intake, the former was adjusted for the latter using the residuals from linear regression models. For this analysis, subjects were divided into three groups according to the tertile of energy-adjusted nutrient intakes among controls.

The latency period for ALS may be longer than a few years. To address the possibility that changes in lifestyle due to the progression of ALS might have affected the results, we asked subjects whether they had altered their lifestyle, including dietary habits, from three years before the onset of ALS to the date of the study. We also excluded participants with a change in lifestyle, extreme daily energy intakes (<800 or >4000 Kcal for men and <500 or >3500 for women) or incomplete FFQ.

Results

A total of 194 consecutive patients with ALS were identified from the study hospitals. Among them, 31

Table I. Selected background characteristics of study subjects.

	Cases (n=153)	Control (n=306)	
	% or mean	% or mean	p-value
Sex			
Men	60.3	60.3	
Women	39.7	39.7	
Age group			
−49	32.6	33.3	
50–59	36.4	34.8	
60+	31.0	31.9	
Mean age (SD)	63.7±9.2	63.4±10.6	0.05
BMI	22.2±0.2	23.3±0.3	<0.05
Type A behavior pattern	44.2	19.6	0.000
Energy intake (Kcal/day)			
<1554	32.7	24.8	
1554–1987	20.5	24.8	
1987–2418	21.6	24.8	
>2418	25.1	25.8	

were excluded because they met the above exclusion criteria, resulting in 153 ALS patients available for the present analysis. Table I shows the characteristics of cases and controls. The mean ages were around 63.0 years, accounting for about 60% of the men among ALS patients and community controls. The proportion of proxy interviews was similar between ALS patients and controls.

Table II summarizes the ORs for ALS by daily nutrient intake. Carbohydrate intake was positively associated with the risk of ALS. ORs of the former from the second to the highest tertile were 1.51 and 2.14 (95% CI 1.05–4.36; trend p=0.04), respectively. The risk of ALS was significantly reduced with a higher intake of total fat. ORs for the second and third tertile were 0.57 and 0.41 (95% CI 0.21–0.80; trend p=0.008), respectively. For fatty acids, ORs for the highest tertile of intake versus the lowest were 0.30 (95% CI 0.16–0.58; trend p=0.04) for saturated fatty acids (SFAs), 0.35 (95% CI 0.18–0.69; trend p=0.003) for monounsaturated fatty acids (MUFAs), and 0.58 (95% CI 0.40–0.96; trend p=0.044) for polyunsaturated fatty acids (PUFAs). The percentage of total energy to carbohydrate was significantly associated with an increased risk of ALS, while that to total fat was significantly associated with a reduced risk of ALS.

Discussion

In the case-control study of SAH, we found higher intake of carbohydrate, and lower intakes of total fat, SFAs, and MUFAs were significantly associated with an increased ALS risk. To the best of our knowledge, no epidemiological information was available about the relationship between macronutrients and the risk of ALS. This is the first epidemiological finding that a high intake of carbohydrate may be a risk factor for

Table II. Odds ratios (ORs) and 95% confidence intervals (CIs) for ALS by tertiles(T1–T3) of daily nutrient intakes.

	Cut points (g)*		OR (95% CI)‡			
	T1/T2	T2/T3	T1	T2	T3	Trend p
Protein (g)	59.1	81.7	1.00	0.97 (0.56–1.66)	0.77 (0.36–1.65)	0.50
Fat (g)	44.9	65.7	1.00	0.57 (0.34–0.95)	0.41 (0.21–0.80)	0.008
Carbohydrate (g)	230.8	295.4	1.00	1.51 (0.89–2.58)	2.14 (1.05–4.36)	0.042
SFA (g)	12.0	18.6	1.00	0.64 (0.39–1.02)	0.30 (0.16–0.58)	0.038
MUFA (g)	15.4	23.7	1.00	0.71 (0.43–1.17)	0.35 (0.18–0.69)	0.003
PUFA (g)	11.1	15.2	1.00	0.85 (0.51–1.42)	0.58 (0.40–0.96)	0.044
n-3 fatty acids (g)	2.0	2.8	1.00	0.75 (0.46–1.21)	1.14 (0.70–1.87)	0.61
n-6 fatty acids (g)	7.3	10.1	1.00	0.82 (0.51–1.31)	1.24 (0.80–1.92)	0.31
n-6/ n-3	3.5	4.1	1.00	0.75 (0.47–1.21)	1.11 (0.71–1.72)	0.24
Percent of total energy						
Carbohydrates	13.1	15.1	1.00	1.63 (0.96–2.75)	2.90 (1.77–4.76)	0.000
Fat	22.7	28.3	1.00	0.96 (0.62–1.46)	0.39 (0.24–0.66)	0.001
Protein	50.4	57.8	1.00	0.75 (0.48–1.16)	0.68 (0.39–1.05)	0.069

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids. *Adjusted to a mean energy intake of 2122 Kcal/d (8882 KJ/d). ‡Adjusted for age, gender, BMI, and behavior pattern.

ALS, whereas a high intake of total fat, SFA and PUFA may protect against the onset of ALS. We also observed as statistically significant an approximately 60% reduction in ALS risk in the highest category of total fat intake compared with the lowest, and that inverse relationship remained even after adjusting for confounding factors.

A methodological issue in this study was how we used FFQ to assess nutritional status. Since our FFQ used was not designed to examine the amount of selected foods intake, we did not test for the reproducibility of each frequency of consumption of selected foods. Drewnowsk et al. reported that mean frequencies of food consumption were a significant predictor of dietary outcomes (19). Their findings strongly suggest that a misclassification may not be serious enough to produce a spurious positive or inverse association. In this study, we added BMI into the model. Moreover, we added BMI into the model as confounding factor. This was because BMI was significantly higher in cases than in controls, and had a positive association with several nutritional factors, but this was not significant. These findings suggest that BMI may confound for the relationship between nutritional factors and the risk of ALS.

In this study, we have no clear explanation as to the underlying mechanisms for the observation that a higher intake of carbohydrate increases the risk of ALS, while a higher intake of total fat, SFA or PUFA reduces it. For carbohydrate intake, several studies have demonstrated that high glucose promotes apoptotic cell death through the production of free radicals, oxidant stress and reactive oxygen species (20,21). Carbohydrate metabolism was impaired in patients with motor neuron disease and spinocerebellar disease (24), while low glucose affected cell growth and survival (25).

Concerning total fat intake, several experimental studies have demonstrated that total fat and fatty acid type intake such as SFA, MUFA and PUFA has a neuroprotective effect (26–32).

These experimental findings might provide an explanation as to the mechanism underlying the relationship between high carbohydrate and low fat intake and the risk of ALS. Taking these results into account, our findings speculate that the production of oxidative stress induced by a high intake of carbohydrate and the decrease in or lack of an antioxidant defense induced by a low intake of total fat and some kinds of fatty acids may, in combination, increase the risk of ALS. Moreover, our investigations also revealed that a high carbohydrate and low fat intake might play an important role in the development of ALS among humans.

There are several limitations to this study. First, we used prevalent cases where diagnosis was made within four years before the present study, which might cause them some difficulty in recalling their conditions before the onset of ALS. In this study, information on the average habitual intake frequency was self-reported retrospectively in both ALS patients and controls. Patients may have reason to recall or learn about a lifestyle in greater detail than controls. Moreover, since our questionnaire asked for much information appertaining to three years before recruitment into the study, some may have reported dietary habits already altered by the onset of ALS. To avoid such problems, we confirmed no change in their lifestyle during the three years before the onset of symptoms. This was necessary because differential recall and misclassification seemed to be proportional to the length of the period from the onset to the interview. These findings could lead to a misclassification of their true long-term dietary exposure and a weakening of their observed associations.

Secondly, we used a self-administered questionnaire to collect information from both cases and controls. The authors have discovered no significant difference in the responses to questions related to lifestyle factors such as physical activity, general life stress and dietary habit between self- and interviewer-administered questionnaires (33). Marshall et al. reported that 90% of the estimates by spouses and by respondents to food-frequency questionnaires are within one frequency category of each other (34). In our study, associations between macronutrients and ALS occurrence still remained after excluding the data obtained from proxy respondents (data not shown). These findings suggest that the effect of our collection method on subjects' responses would be minimal.

Our current investigation had methodological strengths that were identified according to the most recent diagnostic criteria, and adjustment was made for extensive potential confounders.

In summary, the present study suggests that high intakes of carbohydrate and low intakes of fat may, when combined, increase the risk of ALS. Larger studies with more detailed information are needed to draw a firm conclusion on whether fat intake, including fatty acids, confers protection against ALS in Japan. Further investigations of Western populations are also required to assess the effects of macronutrients on ALS.

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Statistical Data

Comparison of the Clinical Features of Japanese Patients with Primary Biliary Cirrhosis in 1999 and 2004: Utilization of Clinical Data When Patients Applied to Receive Public Financial Aid

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BACKGROUND: In Asia there are few reports considering time intervals in the examination of clinical features of primary biliary cirrhosis (PBC). Therefore, we tried to compare the characteristics of patients with PBC in two different years.
METHODS: In two fiscal years (1999 and 2004), 9,761 and 13,142 patients with symptomatic PBC were registered to receive public financial aid from the Ministry of Health, Labour and Welfare of Japan, respectively. For the present study, clinical data from 2,127 patients in 1999 and 6,423 ones in 2004 were available. We compared the data in the two different years, including sex, age, major symptoms, and laboratory data.
RESULTS: Male/female ratios were the same figure (0.13 for 1999 and 2004). The median age was significantly older in 2004 than in 1999 (59 years for 1999, 63 years for 2004, respectively, $p<0.01$). Jaundice and esophageal varices were found significantly less frequent in 2004 than in 1999 ($p<0.01$ for each item). Levels of total bilirubin, γ-glutamyl transpeptidase (γ-GTP), total cholesterol, and immunoglobulin M were significantly lower in 2004 than in 1999 ($p< 0.02$ for total bilirubin, and $p<0.01$ for other each item). The positive rate of antimitochondrial antibodies was significantly higher in 1999 than in 2004 (87.0% for 1999, 83.5% for 2004, respectively, $p<0.01$)). Complicated autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and chronic thyroiditis were found significantly more frequent in 2004 than in 1999 ($p<0.01$ for each item).
CONCLUSIONS: Among the patients with PBC in 2004, an increase in median age, and lower levels of laboratory data such as γ-GTP have been found compared to 1999. These results may show an accumulation of patients with better prognosis and the recent medical progress in controlling patients with PBC.
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Key words: Liver Cirrhosis, Biliary; Public Financial Aid; Clinical Findings; Laboratory Findings; Antimitochondrial Antibodies.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disorder characterized by the progressive, nonsuppurative inflammation and destruction of small bile ducts, and the presence of antimitochondrial antibodies (AMA) in the sera. PBC is considered to be associated with disturbances in both cellular and humoral immunity.[1] There are two known clinical types of PBC, i.e, one is asymptomatic PBC which shows no symptoms of hepatic disorder, and the other is symptomatic PBC which has various clinical symptoms and signs, such as pruritus and jaundice.[1,2] In Japan symptomatic PBC was specified as one of "the intractable diseases" from 1990. Patients with symptomatic PBC who want to receive public financial aid for the treatment from the Ministry of Health, Labour and Welfare must sign agreements and write applications. Then they are registered and can receive public

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financial aid. The recognition of patients with symptomatic PBC is conducted by each prefecture.

Although PBC has been described in virtually all parts of the world,[3] most of the epidemiologic data have been derived from Europe,[4,5] and in Asia, and there are few reports considering time intervals in the examination of clinical features of PBC. Previously our cross-sectional study showed clinical futures of Japanese patients with PBC in 1999.[6] In the present study, we tried to compare the characteristics of patients with PBC in two different years by utilization of the clinical data when they applied to receive public financial aid.

METHODS

In the present study, patients whose conditions met one of the criteria below were diagnosed as having PBC following the previous reports in Japan.[7,8]

1. Chronic non-suppurative destructive cholangitis (CNSDC) is histologically observed, and laboratory data do not contradict PBC.
2. AMA is positive. CNSDC is not histologically observed, but histological findings are compatible with PBC.
3. Histological examination is not performed, but AMA is positive, and clinical findings and course indicate PBC.

For the patients with symptomatic PBC, the following information was collected from the records: sex, date of birth, date of diagnosis, estimated onset time, symptoms and physical findings, complicated autoimmune diseases, laboratory data including serum levels of total bilirubin, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), total cholesterol (T-Chole), immunoglobulin M (IgM), and AMA.

In fiscal year 1999, 9,761 prevalent cases with symptomatic PBC were registered. We could obtain clinical data of 6,527 patients from the Research Committee of Intractable Hepatic Diseases. From 2001, the Ministry of Health, Labour and Welfare started inputting data of patients with intractable diseases collected from prefectures in Japan, and from 2004 electric devices including those clinical data were available. Before 2002, patients with intractable disease applied for financial aid every three years, but after 2003 they have to apply for it every year. In the fiscal year of 2004, 13,142 prevalent cases with symptomatic PBC were registered, and we were permitted to use the clinical data of 6,423 patients provided from the Ministry of Health, Labour and Welfare. Unfortunately, we could not access all of the data from registered patients with PBC in those two years because several prefectures did not provide the data and there were many blank spaces in data regarding resident areas of the patients in 1999. Therefore, 2,127 cases in 1999 and 6,423 cases in 2004 who lived in the same prefecture (32 prefectures) were used to examine for the present study.

We compared symptoms and physical findings, laboratory data, and complicated autoimmune diseases in 1999 and 2004. In the present study, frequencies of items in the clinical data were analyzed, excluding "unclear" or blank spaces. Statistical analysis was performed using SPSS® version 13 (SPSS Inc.). The chi-square test was used for comparing the proportions of two groups, and the Mann-Whitney test was used to evaluate differences in clinical variables. $P < 0.05$ was considered significant.

RESULTS

Sex and Age

Table 1 presents the demographic characteristics of the patients with PBC examined in this study. The male/female ratios were the same figure (0.13 for 1999 and 2004). The median ages of the patients in 1999 and 2004 were 59 and 63 years, respectively. The median age of the patients with PBC was significantly older in 2004 than in 1999 ($p<0.01$). The highest frequencies were in the 60s for the two years (33.2% in 1999 and 33.9% in 2004, respectively). The proportion of the groups aged 20-69 years decreased, while the groups aged 70 years or older increased in 2004 compared to 1999.

Symptoms and Physical Findings

In 1999, pruritis was present in 55.5%, jaundice in 11.8%, and esophageal varices in 21.4% of the patients. While, in 2004, pruritis was present in 57.5%, jaundice in 7.2%, and esophageal varices in 16.5% (Table 2). Statistical significance was not found in the proportion of pruritis, but jaundice and esophageal varices were found significantly less frequently in 2004 than in 1999 ($p<0.01$ for each item).

Laboratory Data

Key laboratory data are summarized in Table 3. Levels of total bilirubin seemed to be almost the same among the patients in 1999 and 2004. We calculated 95 percentiles of the levels of total bilirubin for the two years and found that they were 3.0 mg/dL in 1999 and 2.2mg/dL in 2004, respectively. Regarding levels of ALP, significant difference did not exist between the two years. Whereas levels of γ-GTP, T-Chole, and IgM were significantly lower in 2004 than in 1999 ($p<0.01$ for each item). The positive rate of AMA was significantly higher among the patients in 1999 than in 2004 (87.0% for 1999, 83.5% for 2004, respectively, $p<0.01$).

Complicated Autoimmune Diseases

Complicated autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and chronic thyroiditis were found significantly more frequently in 2004 than in 1999 (17.0%, 7.3%, and 4.7% in 1999, 20.7%, 10.3%, and 12.4% in 2004, respectively, $p<0.01$ for each item) (Table 4).

DISCUSSION

In Western countries, it has been reported that 90% to 95% of patients with PBC are women, with the median age at the time of

Table 1. Demographic characteristics of the patients with primary biiary cirrhosis in 1999 and 2004.

	1999	2004	P value
Number of subjects	n=2,127	n=6,423	
Male/Female ratio	0.13 (250/1,877)	0.13 (753/5,670)	
Age (median, interquartile range)	59 years (51-67)	63 years (55-70)	<0.01*
Age(year) (%)			
-19	2 (0.1)	8 (0.1)	
20-29	10 (0.5)	33 (0.5)	
30-39	58 (2.7)	128 (2.0)	
40-49	322 (15.1)	555 (8.6)	
50-59	692 (32.5)	1,801 (28.0)	
60-69	707 (33.2)	2,175 (33.9)	
70-79	300 (14.1)	1,476 (23.0)	
80+	36 (1.7)	247 (3.8)	
Total	2,127 (100)	6,423 (100)	

*: Mann-Whitney test for 1999 vs. 2004

Table 2. Prevalence of selected symptoms and physical findings among patients with primary biliary cirrhosis in 1999 and 2004.

	1999	2004	P value*
Pruritus	55.5% (1,154/2,080)	57.5% (3,664/6,371)	0.10
Jaundice	11.8% (248/2,094)	7.2% (454/6,348)	<0.01
Esophageal varices	21.4% (397/1,857)	16.5% (1,002/6,072)	<0.01

*: Chi square test for 1999 vs. 2004

Table 3. Laboratory findings of patients with primary biliary cirrhosis in 1999 and 2004.

	1999		2004		
	Median	Interquartile range	Median	Interquartile range	P value*
Total Bilirubin (mg/dL)	0.6 (n=2,127)	0.5 - 1.0	0.7 (n=6,248)	0.5 - 0.9	0.02*
ALP (IU/L)	363 (n=2,108)	241 - 569	360 (n=6,317)	263 - 511	0.72*
γ -GTP (IU/L)	87 (n=2,127)	38 - 198	62 (n=6,328)	31 - 133	<0.01*
Total Cholesterol (mg/dL)	202 (n=2,127)	172 - 231	197 (n=5,860)	171 - 223	<0.01*
IgM (mg/dL)	360 (n=1,690)	221 - 571	242 (n=4,096)	157 - 373	<0.01*
AMA positivity	87.0% (1,761/2,023)		83.5% (3,932/4,710)		<0.01**

*: Mann-Whitney test for 1999 vs. 2004

**: Chi square test for 1999 vs. 2004

AMA: antimitochondrial antibody

Table 4. Prevalence of complicated autoimmune diseases among patients with primary biliary cirrhosis in 1999 and 2004.

Autoimmune diseases	1999	2004	P value*
Sjögren's syndrome	17.0% (310/1,827)	20.7% (895/4,322)	<0.01
Rheumatoid arthritis	7.3% (146/2,005)	10.3% (395/3,822)	<0.01
Chronic thyroiditis	4.7% (99/2,127)	12.4% (487/3,914)	<0.01

*: Chi square test for 1999 vs. 2004

diagnosis in the early 50s.[9-11] In Japan, the Research Committee on the Epidemiology of Intractable Diseases conducted two rounds of nationwide surveys of PBC in 1992 and 1997.[12,13] These surveys reported that the male/female ratio was 0.11 in 1992 and 0.12 in 1997, respectively. The male/females ratios in the present study were 0.13 in 1999 and 2004 so that these ratios were considered to be in approximate agreement with the two reports from the previous nationwide surveys in Japan. The median age of the patients with PBC was significantly older in 2004 than in 1999 (59 years in 1999 and 63 years in 2004, respectively). The main reason regarding this increase of median age was that the proportion of the groups aged 20-69 years decreased but in contrast the groups aged 70 years or older increased in 2004 compared to 1999. One of the explanations of the increase of median age may owe to an accumulation of patients with better prognosis and the recent medical progress in controlling patients with PBC.

Jaundice and esophageal varices were found significantly less frequently in 2004 than in 1999. The decrease of frequencies of jaundice and esophageal varices could be explained by several reasons. It was reported that such severe PBC patients who have levels of bilirubin 2+mg/dL seemed not to survive a long time and their 5-year survival rate was 53% in Japan.[3] Therefore, we tried to compare proportions of patients having levels of bilirubin 2+mg/dL between 1999 and 2004, and could find that the proportion in 1999 was higher than in 2004 (9.0% and 5.9%, respectively). From this result, it is considered that the patients with a high level of bilirubin who often had esophageal varices died within 5 years and the frequency of jaundice in 2004 decreased. It is well known that an elevated bilirubin level is an important prognostic value among the patients with PBC.[3]

Recently, usage of ursodeoxycholic acid (UDCA) is a very common treatment for PBC, and it is known that UDCA lowers the serum level of ALP and γ -GTP, especially among the patients of early stage of PBC.[14-16] In our results, levels of γ -GTP and IgM were significantly lower in 2004 than in 1999, although the level of ALP did not decrease. Usage of UDCA is now common in Japan as well as in western countries; thus UDCA might be effective to lower the level of γ -GTP in the present study. The mechanism of effects of UDCA is still unclear, but it is considered that the drug may have cytoprotective and choleretic effects and alters the bile pool by competition for uptake by ileal bile acid receptors.[3] In the present study, the 95 percentile of the level of total bilirubin was higher in 1999 than in 2004, thus more frequency of patients with high bilirubin level in 1999 was considered a main reason for significant difference between the two years.

The positive rate of AMA was significantly higher among the patients in 1999 than in 2004. Previously, Michieletti et al. described patients with features like PBC in whom serum AMA was negative and antinuclear antibodies were positive,[17] and they suggested a subgroup termed autoimmune cholangitis. AMA is generally examined by the immunofluorescence method (IF) and/or by enzyme-linked immunosorbent assay (ELISA),[18,19] and AMA in the present study was also examined by IF and/or ELISA. Therefore, assessment of the positivity of AMA is thought to be reliable, and it may be possible that AMA negative patients belong to autoimmune cholangitis. We have already reported AMA negative patients with PBC in 1999 among Japanese[20] who showed a lower level of serum IgM. In the present study, the level of IgM was lower in 2004 than in 1999. However, we cannot immediately conclude that the number of the patients with autoimmune cholangitis is gradually increasing because we could not obtain adequate information about histopathology findings in 2004.

Complicated autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and chronic thyroiditis were found significantly more frequent in 2004 than in 1999. In Western countries it is reported that Sjögren's syndrome, rheumatoid arthritis, and thyroid diseases are found in 20%, 10% to 20%, and 10 to 15% of patients with PBC, respectively.[1,10,11] Our AMA negative patients with PBC in 1999 had higher frequencies of complicated autoimmune diseases than AMA positive patients.[20] These higher frequencies of complicated autoimmune diseases may also suggest increases of autoimmune cholangitis

The present study has some limitations. Firstly, we could not access all of the data from registered patients with PBC because several prefectures did not provide the data. Moreover, there were many blank spaces in data regarding resident areas of the patients in 1999, and only 2,127 cases were available. Secondly, we could not completely discuss the AMA negative patients with respect to autoimmune cholangitis because we could not obtain the histological information for all of the patients in 2004. Finally, we compared the cross-sectional clinical features of the patients with PBC in different two years, but comparison of the same patients during some periods is more desirable when we want to know the clinical courses of the patients with PBC. Therefore, we are planning to examine corresponding patients at different points in time.

In conclusion, among the patients with PBC in 2004, an increase in median age, and lower levels of laboratory data such as γ -GTP have been found compared to 1999. These results may show an accumulation of patients with better prognosis and the recent medical progress in controlling patients with PBC.

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